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## HEART REMODELING AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON RENAL REPLACEMENT THERAPY

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## РЕМОДЕЛИРОВАНИЕ СЕРДЦА И КАЧЕСТВО ЖИЗНИ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК, ПОЛУЧАЮЩИХ ЗАМЕСТИТЕЛЬНУЮ ПОЧЕЧНУЮ ТЕРАПИЮ

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The correlation between structural and hemodynamic parameters of the heart and Quality of life (QOL) parameters have been studied in chronic kidney disease (CKD) patients on hemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD) and kidney transplant recipients (KTR). Patients were divided into three groups according to the type of RRT. CKD stage 3 patients were in the control group.

The significant correlation has been founded between the values of the myocardial mass index (LVMI), end-diastolic size (LVEDS), end-diastolic volume (LVEDV), end-systolic size (LVESS), end-systolic volume (LVESV), ejection fraction (LVEF) of the left heart ventricle and QOL among patients on RRT with minimal structural and functional changes in the heart. A negative correlation has been founded between LVMI, LVEDS, LVEDV and physical health component (PF). A decrease in LVEF, as well as an increase in LVESS and LVESV, was associated with the deterioration in both indicators of physical (PF, RP) and psychological health (SF).

*Keywords: quality of life, renal replacement therapy, structural changes in the left heart ventricle*

У больных с хронической болезнью почек (ХБП), находящихся на лечении гемодиализом (ГД), постоянным амбулаторным перитонеальным диализом, и у реципиентов аллотрансплантации почки (АТП) наблюдалась взаимосвязь структурных и гемодинамических показателей сердца с параметрами качества жизни (КЖ) при достигнутых целевых клинико-лабораторных значениях заместительной почечной терапии (ЗПТ). В исследовании включены пациенты с ХБП 3, выделенные в подгруппы по методу ЗПТ. В контрольную группу вошли пациенты с ХБП 3.

При минимальных структурно-функциональных изменениях сердца у больных, получающих ЗПТ, выявлена достоверная взаимосвязь между значениями индекса массы миокарда левого желудочка (ИММЛЖ), конечно-диасто-

лического размера (КДР), конечно-диастолического объема (КДО), конечно-систолического размера (КСП), конечно-систолического объема (КСО), фракции выброса левого желудочка сердца и КЖ. Установлена отрицательная корреляционная взаимосвязь ИММЛЖ, КДР, КДО с показателями физического здоровья.

Снижение фракции выброса, а также увеличение КСП и КСО ассоциировались с ухудшением как показателей физического, так и психологического здоровья.

*Ключевые слова:* качество жизни, заместительная почечная терапия, структурные изменения миокарда левого желудочка

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BMI – body mass index  
BP – bodily pain  
CAPD – continuous ambulatory peritoneal dialysis  
CKD – chronic kidney disease  
GH – general health  
HD – hemodialysis  
KTR – kidney transplant recipients  
LVEDS – left ventricular end-diastolic size  
LVEDV – left ventricular end-diastolic volume  
LVEF – left ventricular ejection fraction  
LVESS – left ventricular end-systolic size  
LVEVS – left ventricular end-systolic volume  
LVH – left ventricular myocardial hypertrophy

LVMI – left ventricular mass index  
MH – mental health  
MV – minute volume  
PCH – physical component of health  
PF – physical functioning  
PsCH – psychological component of health  
QOL – quality of life  
RE – role-emotional  
RP – role-physical  
SF – social functioning  
SV – stroke volume  
VT – vital activity

**C**ardiovascular complications are the leading cause of death of CKD patients on RRT. Size and weight changes of the left ventricle of heart generally represent manifestations of cardiomyopathy in CKD. The frequency of structural and functional changes in the left ventricle of heart in patients on RRT is 85 %, which is more often than in the general population [1, 2]. It is a well-known fact that left ventricular myocardial hypertrophy (LVH) is a significant predictor of mortality and cardiovascular complications in the general population, as well as in patients with CKD [3, 4]. The prevalence of LVH in patients on HD or CAPD achieves 75–85 %, and in kidney transplant recipients (KTR) – 50–70 % [1].

The LVH progression depends on many factors. Arterial hypertension, anemia, hemodynamic overload, as well as neurohumoral changes, are the leading causes which lead to LVH in patients with CKD, especially in patients on RRT [1, 5, 6]. It is known, that anemia is a predictor of complications and mortality of cardiovascular diseases in patients with CKD. Also, it is a factor that contributes to the LVH development [7]. Kinds of research discovered increases in mortality from cardiovascular complications among patients on RRT with bad nutritional status [8, 9].

The QOL indicators are getting worse during CKD progression. It is known that a low level of physical and psychological health components are independent factors of survival, as well as the risk of fatal cardiovascular events in dialysis patients [10]. QOL indices of kidney transplant recipients are usually higher than in dialysis patients [11, 12]. The existence of cardiovascular symptoms in patients with CKD at the pre-dialysis stage is associated with the deterioration in QOL parameters [13]. The interconnection of structural and functional changes in the myocardium with QOL indicators has not been studied enough. We have not found the investigations for possible correlation of the structural and functional heart parameters and QOL in patients on HD, CAPD, and kidney transplant recipients when the main clinical and laboratory parameters were achieved. Therefore, the goal of the study was to correlate the severity

of structural changes in the left ventricle of the heart with the QOL parameters in patients on RRT and kidney transplant recipients, when the main target clinical and laboratory parameters of the treatment have been achieved.

**Material and Methods.** Based on inclusion/exclusion criteria, sixty-five end-stage CKD patients were selected to cross-sectional study after signing the informed consent. Subsequently, three groups were formed. The first group consists of patients who receive HD (n=23). The second group included patients receiving CAPD (n=22). The other twenty kidney transplant recipients formed the 3rd group.

Patients with CKD 3 were selected as a control group (n=21). The groups were comparable in age, RRT duration, body mass index (BMI), continuance, and level of arterial hypertension ( $p>0.05$ ). The average age of patients in the first group was  $48.57\pm 1.99$  years, in second group –  $46.05\pm 2.20$  years, in third group –  $43.2\pm 2.21$  years, in control group –  $46.14\pm 1.55$  years. BMI is 25.64 (3.61) in first group, 26.73 (4.34) in second group, 24.91 (5.23) in third group, and 25.05 (4.51)  $\text{kg}/\text{m}^2$ , with no significant difference from control group ( $p>0.05$ ). The average systolic blood pressure was 134.75 (14.28) mmHg in first group, 137.00 (8.41) mmHg in second group, 125.00 (9.05) mmHg in third group and 134.00 (13.34) mmHg,  $p>0.05$  in the control group. The diastolic blood pressure was 82.35 (6.64); 84.72 (9.47); 80.77 (7.60) and 86.00 (7.54) mm Hg respectively;  $p>0.05$ . The patients with renal failure, caused by chronic glomerulonephritis, polycystic kidney disease or chronic pyelonephritis in the inactive phase, and kidney transplant recipients without clinical and laboratory signs of kidney transplant pathology were included in the research.

The inclusion criteria were the absence of clinical and laboratory signs of protein-energy deficiency and the achievement of target hemoglobin levels.  $\text{Kt}/\text{V} \geq 1.2$  was in patients on HD and  $\geq 1.7$  in patients on CAPD. Several criteria have been used to show the absence of protein-energy deficiency: BMI over 19.5  $\text{kg}/\text{m}^2$ ; the thickness of the skin fold above the triceps for men more than 9.5 mm, for women more than 13 mm; the circumference of the shoulder muscles for men more

than 23 cm, for women more than 21 cm; the level of albumin and total blood protein more than 35 g/l and 65 g/l respectively [14]. The investigation did not include patients older than 60 years, patients with heart disease, persistent uncontrolled hypertension during the last six months, with symptoms of an acute cerebrovascular accident during the previous six months. The presence of diabetes mellitus, connective tissue systemic diseases, oncological diseases, chronic obstructive pulmonary disease in history, the presence of decompensation signs of secondary hyperparathyroidism served as exclusion criteria from the investigation.

All patients underwent an echocardiographic study. The sizes of the left ventricle were estimated by indicators of LVEDR, LVESR, LVEDV, LVESV. The systolic function of the left ventricle was evaluated by signs of stroke volume (SV), minute volume (MV), and LVEF. LVH was established with a level of LVMI for men more than 134 g/m<sup>2</sup> and for women more than 110 g/m<sup>2</sup> [15].

We used the SF-36 questionnaire (Short-Form-36), consisting of 8 scales (each from 0 to 100 points) to determine QOL. The best QOL was assessed with the maximum number of points on each scale. The physical component of health (PCH) was evaluated according to the following scales: «physical functioning» (PF), «role-physical» (RP), «bodily pain» (BP), and «general health» (GH). The following scales evaluated the psychological component of health (PsCH): «vital activity» (VT), «social functioning» (SF), «role-emotional» (RE), and «mental health» (MH) [16].

The results of the investigation were evaluated with descriptive statistics indicators. One-way ANOVA was used to establish differences in the groups. Significations of signs are presented in the form of average value and standard deviation M (SD) according to the normality of the distribution. The determinations of correlation are depended on the normality of their distribution: the Spearman coefficient was used for variables with an abnormal distribution, and the Pearson coefficient was used with a normal distribution. Differences when  $p < 0.05$  were considered statistically significant.

**Results and Discussion.** Analysis of echocardiographic parameters (LVEDV, LVESV, LVEDR, LVESR) and systolic function (SV, MV, LVEF) of the left heart ventricle, as well as the calculated indicator (LVMI) characterizing the presence of LVH has been done in the investigated groups. The results are presented in the Table.

An assessment of the parameters of the left heart ventricle showed that the average values of the LVEDR and LVESR in all groups did not exceed the normal level, but in the HD group of patients, they were significantly higher ( $p < 0.05$ ) than in kidney transplant recipients and patients with CKD 3.

It has been founded that the LVESV, LVEDV, and MV in the group of patients on HD were significantly higher ( $p < 0.05$ ) than in kidney transplant recipients and patients with CKD 3, and LVEDV is higher than in patients on CAPD. Moreover, the average LVEDV and LVESV did not exceed the normal levels, and the average MV was higher than the normal level in all studied groups.

The average SV did not exceed the normal level in all studied groups and were comparable with patients

Table  
**Comparative characteristics of the structural and functional parameters of the left heart ventricle in patients on RRT, kidney transplant recipients and patients with CKD 3**

Indicators	Group 1 (patients on HD), n=23	Group 2 (patients on CAPD), n=22	Group 3 (recipients of kidney transplant), n=20	Group 4 (patients with CKD 3), n=21	p
LVEDR, mm					
M (SD)	52.62 (7.08)	48.21 (4.95)	47.49 (3.54)	47.34 (4.34)	$p_{1,3} < 0.05$
Median	54.90	48.50	47.55	47.05	$p_{1,4} < 0.05$
LVESR, mm					
M (SD)	32.76 (3.05)	30.06 (4.34)	27.85 (3.19)	28.23 (3.08)	$p_{1,3} < 0.05$
Median	33.15	29.05	27.50	28.40	$p_{1,4} < 0.05$
LVEDV, mm					
M (SD)	129.72 (30.06)	105.47 (20.99)	105.24 (18.63)	105.00 (22.17)	$p_{1,2} < 0.05$ $p_{1,3} < 0.05$ $p_{1,4} < 0.05$
Median	142.50	106.00	105.00	102.50	
LVESV, mm					
M (SD)	42.25 (11.15)	35.35 (13.19)	29.55 (8.59)	30.45 (8.07)	$p_{1,3} < 0.05$ $p_{1,4} < 0.05$
Median	43.00	32.00	28.00	30.50	
LVSV, mm					
M (SD)	86.06 (23.61)	74.00 (17.35)	75.69 (13.70)	74.55 (16.20)	$p > 0.05$
Median	96.00	72.00	73.75	78.00	
LVMV, l/min					
M (SD)	6.07 (1.57)	5.31 (1.15)	5.07 (0.79)	4.85 (1.22)	$p_{1,3} < 0.05$ $p_{1,4} < 0.05$
Median	5.72	4.88	5.01	4.86	
LVEF, %					
M (SD)	67.58 (3.60)	67.32 (5.84)	71.69 (5.36)	71.16 (3.72)	$p_{2,3} < 0.05$
Median	67.00	68.00	72.42	70.00	
LVMI, g/m <sup>2</sup>					
M (SD)	157.61 (54.43)	138.59 (39.04)	131.72 (30.97)	128.26 (29.63)	$p_{1,4} < 0.05$
Median	129.18	128.71	120.69	133.45	
M (SD)	128.83 (44.43)	111.53 (28.28)	105.43 (17.33)	87.08 (21.86)	$p_{1,4} < 0.05$
Median	129.49	114.29	106.71	84.33	

in the control group. However, this indicator was slightly higher in patients on HD in comparison with other groups ( $p > 0.05$ ). Significant differences in the values of SV between CAPD patients and kidney transplant recipients were not observed.

There was not found any systolic dysfunction in all studied groups, but the LVEF in the group of kidney transplant recipients was the largest and significantly higher ( $p < 0.05$ ) than in patients on CAPD.

The average LVMI between men and women in the groups of patients on RRT was the smallest among kidney transplant recipients. LVMI among patients on HD was slightly higher than in the other groups and significantly higher than in the control group ( $p < 0.05$ ). This explains that patients on HD have more significant volume overload, which leads to increase myocardial hypertrophy more than on other methods of RRT.

The correlation between QOL parameters and parameters of the left heart ventricle was established in patients with CKD 5 on RRT. The significant negative correlations of QOL indicators by the PF scale of the physical health component and the values of the LVEDR ( $r = -0.30$ ;  $p < 0.01$ ), LVEDV ( $r = -0.28$ ;  $p < 0.05$ ) were determined.

Significant negative correlations were established between LVESD, LVESV and the indicators of the physical QOL component on the following: PF ( $r=-0.34$  ( $p<0.01$ ) and  $r=-0.32$  ( $p<0.05$ ), respectively), RP ( $r=-0.27$  ( $p<0.05$ ) and  $r=-0.26$  ( $p<0.05$ ), respectively) and PCH ( $r=-0.30$  ( $p<0.01$ ) and  $r=-0.29$  ( $p<0.05$ ), respectively). The significant negative correlation have been founded with the indicators of psychological health only by the SF scale and indicators of LVESD ( $r=-0.22$ ;  $p<0.05$ ) and LVESV ( $r=-0.21$ ;  $p<0.05$ ).

A significant positive correlation was established between the LVEF values and the QOL indicators by the PF scale ( $r=0.23$ ;  $p<0.05$ ), by RP scale ( $r=0.23$ ;  $p<0.05$ ), PCH ( $r=0.26$ ;  $p<0.05$ ), by the SF scale ( $r=0.26$ ;  $p<0.05$ ). Significant negative correlations were established between the level of LVMI and indicators of the physical health component: by the PF scale ( $r=-0.36$ ) and PCH ( $r=-0.24$ ,  $p<0.01$ ) in patients with CKD 5.

Thus, it was shown that the main deterioration in patients with CKD 5 was LVH, despite the previous absence of cardiovascular pathology and achievement of the target clinical and laboratory parameters of treatment. The highest values of LVMI were observed in patients on HD and CAPD. Moreover, as in some other studies, the severity of LVH was higher in patients on HD [17, 18]. The mean LVMI values were normal in kidney transplant recipients, regardless of gender. Most likely, this is since the severity of LVH tends to decrease in patients after kidney transplantation [19, 20, 21].

The increase of the LVMI, as well as the left ventricle size, was associated with the decrease of physical activity and exercise tolerance, which was reflected in the overall assessment of the physical health in patients on RRT. An increase of the final systolic size and volume of the left ventricle, as well as a decrease in LVEF, were associated not only with a deterioration in physical health indicators but also with a limitation of social contacts, which can affect the patient's self-esteem.

**Conclusions.** Thus, structural and functional changes of the left ventricle parameters were less in the group of kidney transplant recipients in comparison with the group of patients on dialysis despite that the target clinical and laboratory parameters of the treatment have been reached.

A significant correlation was found between echocardiographic parameters and QOL in patients on RRT compensated by most factors usually affecting the QOL (dialysis adequacy, the achievement of the target hemoglobin level, absence of protein-energy insufficiency, stable blood pressure).

Regular assessment of the structural and functional heart parameters, QOL evaluation, and maintaining the target clinical and laboratory parameters of adequate protein-energy balance and correction of anemia can help to prevent the development of cardiovascular pathology in patients with CKD.

#### Disclosures:

The authors declare no conflict of interest.

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## GENETIC ASPECTS OF THE DEVELOPMENT OF MYOCARDIAL REMODELING IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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## ГЕНЕТИЧЕСКИЕ АСПЕКТЫ РАЗВИТИЯ РЕМОДЕЛИРОВАНИЯ МИОКАРДА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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Currently, one of the prognostic criteria for the development of cardiovascular pathology in type 2 diabetes mellitus (DM) is the patient's genetic characteristics. The study involved 258 patients with type 2 DM, of which 50 were carried out genetic testing with the study of polymorphisms of genes AGT:704, AGTR1:1166, GNB3:825, NOS3:-786, NOS3. The presence of remodeling in patients with DM is associated with an increase in the frequency of registration of NOS3:894 gene polymorphism in the form of a combination of mutation homozygotes and heterozygotes by 27.9 %, heterozygous polymorphism of this gene is associated with the identification of an unfavorable version of left ventricular myocardial remodeling concentric hypertrophy ( $p=0.04$ ). A tendency to an increase in the frequency of the mutation-homozygotes of the gene GNB3:825 by 17.6 % and NOS3:-786 by 26.4 %, as for the heterozygotes of the AGT:704 gene polymorphism by 22.6 % and AGTR1:1166 by 16.7 %.

As a result of our study revealed that the development of structural heart remodeling might be associated with polymorphism of genes encoding NOS3, as well as those responsible for the activity of the ACF: AGT, AGTR1, GNB3. Based on the results of genetic testing, it is possible to assess the prognosis of the disease and rationally select drug therapy, which helps to prevent the development of severe complications of DM.

*Keywords: gene polymorphism, type 2 diabetes mellitus, myocardial remodeling*

В настоящее время одним из прогностических критериев развития сердечно-сосудистой патологии при сахарном диабете (СД) 2 типа являются генетические факторы. В исследовании участвовали 258 пациентов с СД 2 типа, из которых 50 было проведено генетическое тестирование с изучением полиморфизмов генов AGT:704, AGTR1:1166, GNB3:825, NOS3:-786, NOS3. Наличие ремоделирования у пациентов с СД ассоциировано с повышением частоты регистрации полиморфизма гена NOS3:894 в виде сочетания мутации гомозиготы и гетерозиготы на 27,9 %, гетерозигота полиморфизма данного гена ассоциирована с выявлением неблагоприятного варианта ремоделирования миокарда левого желудочка концентрической гипертрофии ( $p=0,04$ ). Выявлена тенденция к увеличению частоты мутации гомозиготы гена GNB3:825 на 17,6 % и NOS3:-786 на 26,4 %, со стороны гетерозиготы полиморфизма гена AGT:704 на 22,6 % и AGTR1:1166 на 16,7 %.

В результате исследования выявлено, что развитие структурного ремоделирования сердца может быть связано с полиморфизмом генов, ответственных за фактор эндотелия (NOS3), а также за активность ангиотензин-превращающего фермента: AGT, AGTR1, GNB3. На основании результатов генетического тестирования возможно определение прогноза заболевания и тактики лекарственной терапии, что способствует предупреждению развития тяжелых осложнений СД.

*Ключевые слова: полиморфизм генов, сахарный диабет 2 типа, ремоделирование миокарда*

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